Clinical trial results:
A Phase I/II Trial Investigating LOAd703 in Combination with Atezolizumab in Malignant Melanoma

Summary

EudraCT number	2019-003300-12
Trial protocol	SE
Global end of trial date	18 July 2023

Results information

Result version number	v1 (current)
This version publication date	05 July 2024
First version publication date	05 July 2024

Trial information

Trial identification

Sponsor protocol code	LOKON003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04123470
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Lokon Pharma AB
Sponsor organisation address	Bredgrand 14, Uppsala, Sweden, 75320
Public contact	Angelica Loskog, Lokon Pharma AB, angelica.loskog@lokonpharma.com
Scientific contact	Angelica Loskog, Lokon Pharma AB, angelica.loskog@lokonpharma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 July 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 July 2023
Global end of trial reached?	Yes
Global end of trial date	18 July 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to determine the tolerability of LOAd703 administered by intratumoral injections in combination with intravenous atezolizumab.

Protection of trial subjects:

The study was conducted in accordance to the protocol, applicable regulatory requirements, GCP and ethical principals of the latest version of the Declaration of Helsinki. The principal investigators were responsible for ensuring the protocol is followed. Safeguards to protect clinical research volunteers include Institutional Review Boards/Independent Ethics Committee, informed consent and cohort review safety meetings.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 September 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 17
Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	24
EEA total number of subjects	17

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	12
From 65 to 84 years	12

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Overall, a total of 26 subjects were enrolled in the study, 2 out of 26 subjects were screening failures and 24 out of 26 subjects were registered in the study. The study enrollment was stopped after obtaining sufficient safety data, and subjects were followed until the End of Study was reached as per protocol.

Pre-assignment

Screening details:

Adult patients (≥18 years of age) with a pathological confirmation of locally advanced or metastatic melanoma who had received at least 1 prior line of checkpoint blockade antibody therapy (monotherapy or combination) as adjuvant or treatment for systemic disease were eligible for the study.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Arm title	Treatment arm

Arm description:

LOAD703 (Delolimogene mupadenorepvec) at two dose levels 1x10e11 VP and 5x10e11 VP in combination with atezolizumab (fixed dose 1200mg). Treatments of LOAd703 (up to 12 times) were delivered by intratumoral injection concurrent with intravenous atezolizumab treatment (up to 19 times) every 3 weeks

Arm type	Experimental
Investigational medicinal product name	LOAd703
Investigational medicinal product code	
Other name	delolimogene mupadenorepvec
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Intratumoral use

Dosage and administration details:

Modified adenovirus serotype 5/35 containing a CMV promoter-driven transgene cassette with human transgenes encoding membrane-bound CD40 ligand (TMZ-CD40L) and full-length 4-1BBL. LOAd703 was tested at two dose levels: 1x10e11VP and 5x10e11 VP. LOAd703 is delivered frozen in vials containing 650 µl of virus in suspension. The frozen vial is thawed at the clinic on wet ice or in a refrigerator +4°C (±2°C) according to the Sponsor's instructions.
The thawed LOAd703 virus is used directly or is diluted with physiological saline (0.9% NaCl)prior use depending on the patient dose and number of lesions to be injected. The Investigator and the radiologist assess together which lesion(s) are suitable for direct or image guided injection. The prescribed virus dose in suspension is administered by i.t. injections into ≤3 lesions per treatment occasion.

Investigational medicinal product name	Atezolizumab
Investigational medicinal product code	
Other name	Tecentriq
Pharmaceutical forms	Concentrate for solution for injection/infusion, Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Humanized monoclonal antibody based on a human IgG1 framework containing heavy chain VHIII and light chain VκI subgroup sequences. For IV administration, atezolizumab (1200mg per vial) is administered in 250 mL IV infusion bags containing 0.9% NaCl and infusion lines equipped with 0.2 or 0.22 um in-line filters. Administration of atezolizumab will be performed in a monitored setting where

there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. No premedication is permitted prior to the first infusion. However, if the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the Investigator.
Atezolizumab will be administrated IV using a fixed dose (1200 mg/infusion).

Number of subjects in period 1	Treatment arm
Started	24
Completed	11
Not completed	13
Consent withdrawn by subject	1
Death (progressive disease)	11
Lost to follow-up	1

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	24	24	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
median	64.0		
inter-quartile range (Q1-Q3)	51.5 to 72.0	-	
Gender categorical Units: Subjects			
Female	11	11	
Male	13	13	
Race Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Black or African American	1	1	
Native Hawaiian or Other Pacific Islander	0	0	
White	21	21	
Other	0	0	
Not reported	2	2	
Ethnicity Units: Subjects			
Hispanic or Latino	1	1	
Not Hispanic or Latino	19	19	
Not reported	4	4	
Disease stage at initial diagnosis Units: Subjects			
stage 0	1	1	
stage I	5	5	
stage II	2	2	
stage III	12	12	

stage IV	3	3	
Unknown	1	1	
Disease stage at study entry Units: Subjects			
stage III	0	0	
stage IV	24	24	
Unknown	0	0	
Time from initial diagnosis Units: months			
arithmetic mean	87.82		
standard deviation	± 98.990	-	

Subject analysis sets

Subject analysis set title	LOAd703 dose 1x10e11 VP
Subject analysis set type	Sub-group analysis
Subject analysis set description: LOAd703 dose is 1x10e11 VP in combination with atezolizumab at fixed dose 1200mg	
Subject analysis set title	LOAd703 dose 5x10e11 VP
Subject analysis set type	Sub-group analysis
Subject analysis set description: LOAd703 dose 5x10e11VP in combination with fixed atezolizumab 1200 mg	

Reporting group values	LOAd703 dose 1x10e11 VP	LOAd703 dose 5x10e11 VP	
Number of subjects	7	17	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
median	70.0	63.0	
inter-quartile range (Q1-Q3)	53.0 to 74.0	46.0 to 70.0	
Gender categorical Units: Subjects			
Female	2	9	
Male	5	8	
Race Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Black or African American	0	1	

Native Hawaiian or Other Pacific Islander	0	0	
White	7	14	
Other	0	0	
Not reported	0	2	
Ethnicity Units: Subjects			
Hispanic or Latino	0	1	
Not Hispanic or Latino	7	12	
Not reported	0	4	
Disease stage at initial diagnosis Units: Subjects			
stage 0	0	1	
stage I	2	3	
stage II	0	2	
stage III	4	8	
stage IV	1	2	
Unknown	0	1	
Disease stage at study entry Units: Subjects			
stage III	0	0	
stage IV	7	17	
Unknown	0	0	
Time from initial diagnosis Units: months			
arithmetic mean	104.85	80.81	
standard deviation	± 143.310	± 78.774	

End points

End points reporting groups

Reporting group title	Treatment arm
Reporting group description:	
LOAD703 (Delolimogene mupadenorepvec) at two dose levels 1x10e11 VP and 5x10e11 VP in combination with atezolizumab (fixed dose 1200mg). Treatments of LOAd703 (up to 12 times) were delivered by intratumoral injection concurrent with intravenous atezolizumab treatment (up to 19 times) every 3 weeks	
Subject analysis set title	LOAd703 dose 1x10e11 VP
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
LOAd703 dose is 1x10e11 VP in combination with atezolizumab at fixed dose 1200mg	
Subject analysis set title	LOAd703 dose 5x10e11 VP
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
LOAd703 dose 5x10e11VP in combination with fixed atezolizumab 1200 mg	

Primary: Safety determined by the NCI-CTCAE v5.0

End point title	Safety determined by the NCI-CTCAE v5.0[1]
End point description:	
End point type	Primary
End point timeframe:	
57 weeks	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical analysis was performed to compare dose groups. Results are presented with descriptive statistics, are tabulated by dose group and reviewed to evaluate the study endpoints.

End point values	LOAd703 dose 1x10e11 VP	LOAd703 dose 5x10e11 VP		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	7[2]	17[3]		
Units: Number of events				
All Adverse events (AE)	52	130		
All Serious adverse events (SAEs)	6	11		
SARs related to LOAd703	0	2		
SARs related to atezolizumab	0	1		
AE leading to withdrawal from the study	0	0		
AE leading to LOAd703 discontinuation	4	4		
AE leading to atezolizumab discontinuation	6	4		
AE leading to death	1	0		
AE related to LOAd703	28	64		
AE related to atezolizumab	20	41		
AE related to LOAd703 and/or atezolizumab	30	72		
AE related to LOAd703 grade 1	17	40		
AE related to LOAd703 grade 2	11	22		
AE related to LOAd703 grade 3	0	2		

AE related to LOAd703 grade 4	0	0		
AE related to LOAd703 grade 5	0	0		
AE related to atezolizumab grade 1	10	26		
AE related to atezolizumab grade 2	10	14		
AE related to atezolizumab grade 3	0	1		
AE related to atezolizumab grade 4	0	0		
AE related to atezolizumab grade 5	0	0		
AE not related to LOAd703 or atezolizumab grade 1	7	32		
AE not related to LOAd703 or atezolizumab grade 2	7	13		
AE not related to LOAd703 or atezolizumab grade 3	7	11		
AE not related to LOAd703 or atezolizumab grade 4	0	2		
AE not related to LOAd703 or atezolizumab grade 5	1	0		

Notes:

[2] - Number of subjects based on safety evaluable population

[3] - Number of subjects based on safety evaluable population

Statistical analyses

No statistical analyses for this end point

Secondary: Best overall tumor response according to RECIST 1.1

End point title	Best overall tumor response according to RECIST 1.1

End point description:

Overall Response Rate is defined as proportion of subjects with the best overall response of complete response (CR) or partial response (PR). Clinical Benefit Rate is defined as proportion of subjects with the best overall response of complete response (CR) or partial response (PR) or stable disease (SD).

End point type	Secondary

End point timeframe:

57 weeks

End point values	LOAd703 dose 1x10e11 VP	LOAd703 dose 5x10e11 VP		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6[4]	15[5]		
Units: Number of subjects				
Complete response	0	0		
Partial response	1	3		
Stable disease	3	6		
Progressive disease	2	6		
Not evaluable	0	0		
Overall response rate (CR or PR)	1	3		
Clinical benefit rate (CR, PR or SD)	4	9		

Notes:

[4] - Number of subjects based on efficacy evaluable population

[5] - Number of subjects based on efficacy evaluable population

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Overall survival

End point title	Overall survival

End point description:

Overall survival is defined as the time from the first dose of study treatment (LOAd703 and/or atezolizumab) until death. In the LOAd703 1 x 10e11 VP + atezolizumab group, the median OS estimate was 26.05 months (95% CI: 2.10, not estimated). In the LOAd703 5 x 10e11 VP + atezolizumab group, the median OS estimate was not reached at the End of Study (25th percentile was 4.40 months [95% CI: 2.56, 12.22]).

End point type	Other pre-specified

End point timeframe:

up till 48 months

End point values	LOAd703 dose 1x10e11 VP	LOAd703 dose 5x10e11 VP		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6[6]	15[7]		
Units: number of subjects				
Number of subjects with event	3	7		
Number of subjects censored	3	8		

Notes:

[6] - Number of subjects based on efficacy evaluable population

[7] - Number of subjects based on efficacy evaluable population

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Progression-free survival

End point title	Progression-free survival

End point description:

Progression free survival is defined as the time from the first dose of study treatment until progression according to RECIST1.1 or death (whichever occurred first). In the 1x10e11 VP LOAd703 + atezolizumab group, the median PFS estimate was 11.19 months (95% CI: 1.84, not estimated); the estimated survival distribution and number of subjects at risk decreased over time (range: 0.6667 to 0, 4 subjects to 0). In the 5x10e11 VP LOAd703 + atezolizumab group, the median PFS estimate was 3.25 months (95% CI: 1.91,6.24); the estimated survival distribution and number of subjects at risk decreased over time (range: 0.5333 to 0.1600, 8 subjects to 2).

End point type	Other pre-specified

End point timeframe:

up to 48 months

End point values	LOAd703 dose 1x10e11 VP	LOAd703 dose 5x10e11 VP		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6[8]	15[9]		
Units: Number of subjects				
Number of subjects with event	5	12		
Number of subjects censored	1	3		

Notes:

[8] - Number of subjects based on efficacy evaluable population

[9] - Number of subjects based on efficacy evaluable population

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Time to progression

End point title	Time to progression

End point description:

Time to progression (TTP) defined as the time from first dose of study treatment until progression according to RECIST v1.1. In the 1 x 10e11 VP LOAd703+atezolizumab group, the median TTP was 11.19 months (95% CI: 1.84, not estimated); the estimated survival distribution and number of subjects at risk decreased over time (range: 0.6667 to 0, 4 subjects to 0). In the 5 x 10e11 VP LOAd703+atezolizumab group, the median TTP was 3.25 months (95% CI: 1.91, 6.24); the estimated survival distribution and number of subjects at risk decreased over time (range: 0.5333 to 0.1600, 8 subjects to 2).

End point type	Other pre-specified

End point timeframe:

57 weeks

End point values	LOAd703 dose 1x10e11 VP	LOAd703 dose 5x10e11 VP		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6[10]	15[11]		
Units: Number of subjects				
Number of subjects with event	5	12		
Number of subjects censored	1	3		

Notes:

[10] - Number of subjects based on efficacy evaluable population

[11] - Number of subjects based on efficacy evaluable population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

57 weeks

Adverse event reporting additional description:

The AE reporting period for this study begins upon recieving the first LOAd703 and/or atezolizumab treatment and continues until final visit at week 57. If a patient experiences an AE after signing the informed consent but before the first treatment, the event may be recorded as medical condition.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	LOAd703 dose 1x10e11VP
Reporting group description: -	
Reporting group title	LOAd703 dose 5x10e11VP

Reporting group description: -

Serious adverse events	LOAd703 dose 1x10e11VP	LOAd703 dose 5x10e11VP	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 7 (28.57%)	5 / 17 (29.41%)	
number of deaths (all causes)	4	7	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Infected neoplasm			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Medication error			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vascular disorders			
Deep vein thrombosis	Additional description: Three events reported in 1 subject: deep venous thrombosis left lower extremity (grade 3); deep venous thrombosis right lower extremity (grade 3), worsening DVT L Leg (grade 3)		
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoedema			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General physical health deterioration	Additional description: SAE of general physical health deterioration (2 events; 1 event Grade 3 that worsened to Grade 5), unrelated to study treatment, led to discontinuation of LOAd703 and atezolizumab in 1 subject. Subject died of disease progression.		
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			

Cytokine release syndrome			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonellosis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	LOAd703 dose 1x10e11VP	LOAd703 dose 5x10e11VP	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	17 / 17 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Tumour pain			

subjects affected / exposed	0 / 7 (0.00%)	2 / 17 (11.76%)	
occurrences (all)	0	2	
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Hypertension			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Hypotension			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Thrombosis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Deep vein thrombosis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 7 (57.14%)	10 / 17 (58.82%)	
occurrences (all)	5	18	
Fatigue			
subjects affected / exposed	1 / 7 (14.29%)	5 / 17 (29.41%)	
occurrences (all)	1	5	
Chills			
subjects affected / exposed	2 / 7 (28.57%)	3 / 17 (17.65%)	
occurrences (all)	3	4	
Injection site pain			
subjects affected / exposed	0 / 7 (0.00%)	2 / 17 (11.76%)	
occurrences (all)	0	2	
Inflammation			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Injection site reaction			

subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Oedema peripheral			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	1 / 7 (14.29%)	2 / 17 (11.76%)	
occurrences (all)	1	2	
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Hiccups			
subjects affected / exposed	1 / 7 (14.29%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Nasal congestion			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Cough			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Dysphonia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Dyspnoea			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Haemoptysis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Hypoxia			

subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Blood creatine increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Blood albumin decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Borrelia test positive			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Lymphocyte count decreased			
subjects affected / exposed	0 / 7 (0.00%)	2 / 17 (11.76%)	
occurrences (all)	0	2	
Neutrophil count decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Troponin I increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
White blood cell count decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	2	
Injury, poisoning and procedural complications			

Infusion related reaction			
subjects affected / exposed	0 / 7 (0.00%)	5 / 17 (29.41%)	
occurrences (all)	0	8	
Contusion			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Rib fracture			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 17 (5.88%)	
occurrences (all)	2	1	
Angina pectoris			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Sinus tachycardia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 7 (14.29%)	4 / 17 (23.53%)	
occurrences (all)	1	8	
Dizziness			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Dysgeusia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Neuropathy peripheral			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Paraesthesia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			

Leukocytosis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Anaemia			
subjects affected / exposed	1 / 7 (14.29%)	2 / 17 (11.76%)	
occurrences (all)	1	5	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	3 / 7 (42.86%)	5 / 17 (29.41%)	
occurrences (all)	6	5	
Vomiting			
subjects affected / exposed	2 / 7 (28.57%)	5 / 17 (29.41%)	
occurrences (all)	2	5	
Diarrhoea			
subjects affected / exposed	0 / 7 (0.00%)	4 / 17 (23.53%)	
occurrences (all)	0	4	
Abdominal pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 7 (28.57%)	1 / 17 (5.88%)	
occurrences (all)	2	1	
Pruritus			
subjects affected / exposed	1 / 7 (14.29%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Erythema			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Skin disorder			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Proteinuria			

subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 7 (0.00%)	3 / 17 (17.65%)	
occurrences (all)	0	3	
Pain in extremity			
subjects affected / exposed	2 / 7 (28.57%)	1 / 17 (5.88%)	
occurrences (all)	2	1	
Groin pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Muscular weakness			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Back pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Muscle spasms			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 7 (28.57%)	1 / 17 (5.88%)	
occurrences (all)	2	1	
Pneumonia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Tooth abscess			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	1 / 7 (14.29%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Hypercalcaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Hyperglycaemia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 17 (11.76%)	
occurrences (all)	0	3	
Hypocalcaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Hypoglycaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Hyponatraemia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 17 (11.76%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 December 2019	Secondary objectives and endpoints (sections synopsis, 3.1, 3.2) • The language is changed to better define what is being evaluated using the objective and endpoints stated. Exclusion criteria (sections synopsis, 4.2): • Criteria 6-12: it is clarified that registration is regarded when the first dose of LOAd703 and atezolizumab is given. • Criteria 18: it is clarified that the contraceptive method must be regarded highly effective, and that abstinence from heterosexual intercourse is a choice of contraceptive method as well depending on the lifestyle of the subject. • Criteria 19: it is clarified that men that has a partner of childbearing potential who refuse highly effective contraceptives are excluded. • Criteria 24: it is added that patients with tested reduced functional respiratory capacity are excluded. Dose limiting toxicity • We added information about the DLT evaluation during dose escalation. • 5.6.1, 5.6.5: we removed the use of Ringer's acetate infusion solution so that all LOAd703 dilutions will be diluted in formulation buffer or physiological saline. • 5.6.3, 5.6.5: we changed that an unopened vial should be used within 24 hours from thawing. Administrative changes
09 January 2020	Administrative changes (EU version 2.1, dated 2020-01-09, was issued to include administrative changes added to the submitted IND version 2.0)
26 March 2020	• Exclusion criteria 15 was clarified to relate to monotherapy with a single PD-1/PD-L1 antibody. Administrative changes: • Section 1.4: The dept of Oncology in Uppsala has a new address. • Section 5.6.3: Temporarily storage of LOAd 703 in -20°C for up to 3 months, has been removed. • Section 5.6.5: the preparation instructions for LOAd703 has been clarified, to clearly state that the maximum dose, injected in 1 lesion, will not be diluted. • Section 5.6.6 was clarified in regards to selection of lesion and that subcutaneous lesions, visible to the eye, may be photographed. • Table I: Overview of ongoing clinical trials was updated. • Section 9.4 Immunological AEs and Handling Plan has been updated to refer to the atezolizumab IB. • Table 3 was removed, which affect the numbering of the 2 subsequent tables.
20 April 2020	• Exclusion criteria 1 was modified so that patients with acral melanoma will not longer be excluded. Administrative change: • A clarification was made in section 2.6.1 so that it is clear that NSAID or steroid treatment can be used.

21 September 2020	Synopsis and section 4.1 Inclusion criteria: • A new criterion was added: A life expectancy of at least 3 months as per the investigator: this is a common inclusion criterion for this type of patients • Patients with locally advanced melanoma or metastatic melanoma can be included, regardless of patient's eligibility for complete tumor resection. • Prior treatment with tyrosine kinase inhibitor(s) is optional; patients that have not yet received treatment with tyrosine kinase inhibitor(s) can be included in the study • Cut-point for serum albumin levels was changed to ≥ 2.5 mg/dL as well as requirement for AST and ALT was changed to ≤ 5 times the ULN if liver metastases are present • Lactate dehydrogenase parameter was removed Synopsis and section 4.2 Exclusion criteria: • Exclusion criteria no 1 was modified so that patients with mucosal melanoma will no longer be excluded. • Exclusion of patients with progressive disease within 8 weeks after checkpoint inhibitor therapy and patients who have had more than 3 lines of treatment; were deemed to be to narrow and was replaced by a criterion excluding patients with rapid progression rate as assessed by the investigator • Exclusion criterion describing number and site of metastases was updated: patients with central nervous system involvement (cerebral metastases) will be excluded, but not patients with bone metastases • Washout period between cytotoxic and radiation therapy and protocol therapy (LOAd703/atezolizumab) was shortened to 14 days • Washout period between immunostimulatory therapy and protocol therapy (LOAd703/atezolizumab) was shortened to 21 days • Patients on warfarin continue to be excluded, but clarification was made that low molecular heparin is permitted Administrative changes
11 November 2020	Changes made in EU version only Synopsis and section 4.1 Inclusion criteria: • Valid for Swedish patients: Patients not eligible for complete resection with locally advanced melanoma or metastatic melanoma can be included. Valid for US patients: Patients with locally advanced melanoma or metastatic melanoma can be included, regardless of patient's eligibility for complete tumor resection. • Valid for Swedish patients: Patients with B-Raf mutations must have received appropriate therapy with tyrosine kinase inhibitors(s) or MEK inhibitor (no changes from version 4.0) Valid for US patients: Prior treatment with tyrosine kinase inhibitor(s) is optional; patients that have not yet received treatment with tyrosine kinase inhibitor(s) can be included in the study
15 February 2021	Changes made in EU version only Substantial change, section 7.2.10: Blood Chemistry and 7.2.11: Hematology: • If samples are taken for routine analysis <7 days prior to screening, the results can be used for eligibility evaluation at the discretion of the investigator, without need of subject the patients for new sampling.

25 April 2022	• Number of patients needed to be enrolled to achieve at least 25 evaluable patients at MTD has been changed to up to 50 throughout the document (synopsis, section 3.3 Summary of Trial Design) • The expected duration of the study has been updated (synopsis, section 3.5 End of Study, 5.0 Treatment of Patients). • An additional site has been added (section 1.0 General Information) • New exclusion criteria no. 32: Adenovirus-based vaccines (e.g Vaxzevria, known as COVID-19 vaccine Astra Zeneca, J&J Covid-19 vaccine) are prohibited 3 months prior to initiation of study treatment, during treatment and 6 months after the final dose of LOAd703 (synopsis, section 4.2, concomitant medication section 5.8). • In section 5.8 Approved and Non-approved concomitant treatment it has been added that palliative surgery and local radiotherapy will be allowed. • The time points for vital signs measurements have been updated in section 5.1 Treatment Overview and 7.2.6 Vital signs. • Addition for US only, as already approved for Sweden. In section 5.1 Treatment Overview and 6.2 Screening, 7.2.10 Blood Chemistry and 7.2.11 Hematology it has been clarified that "If samples are taken for routine analysis <7 days prior to screening, the results can be used for eligibility evaluation at the discretion of the Investigator, without need of subject the patients for new sampling". • Addition for Sweden only. In section 7.3.1 Anti-Adenoviral Antibodies addition of "Valid for Swedish patients: patients enrolled at Uppsala site, Sweden will be asked to provide additional blood samples for research purposes to identify and isolate B-cells producing anti-adenoviral antibodies. Blood samples will be collected at 2-3 occasions (up to 42 ml in total) during the LOAd703 treatment period (starting from week 6 until week 33)" have been made. Administrative changes
09 June 2023	• Definition for the End of study has been modified under section Definition and Terms and in the section 3.5 End of Study and section 13.4 Study Report • The expected duration of the study has been updated to reflect change of the End of Study definition (synopsis, 3.4 Duration of Study, 5.1 Treatment overview) • Contact details for the new Site Principal Investigator at Baylor College of Medicine has been updated. Administrative changes

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Exploratory analysis for shedding, anti-adenovirus immunity, PK atezolizumab, immunity to atezolizumab, immune and protein profile was done. Results are summarized per individual subjects or over time without statistical analysis. Data not submitted.

Notes: